

Fetal cardiac arrhythmias: Current evidence

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ABSTRACT

This article reviews important features for improving the diagnosis of fetal arrhythmias by ultrasound in prenatal cardiac screening and echocardiography. Transient fetal arrhythmias are more common than persistent fetal arrhythmias. However, persistent severe bradycardia and sustained tachycardia may cause fetal hydrops, preterm delivery, and higher perinatal morbidity and mortality. Hence, the diagnosis of these arrhythmias during the routine obstetric ultrasound, before the progression to hydrops, is crucial and represents a challenge that involves a team of specialists and subspecialists on fetal ultrasonography. The images in this review highlight normal cardiac rhythms as well as pathologic cases consistent with premature atrial and ventricular contractions, heart block, supraventricular tachycardia (VT), atrial flutter, and VT. In this review, the details of a variety of arrhythmias in fetuses were provided by M-mode and Doppler ultrasound/echocardiography with high-quality imaging, enhancing diagnostic accuracy. Moreover, an update on the intrauterine management and treatment of many arrhythmias is provided, focusing on improving outcomes to enable planned delivery and perinatal management.

Keywords: Arrhythmias, echocardiography, prenatal diagnosis, ultrasound imaging

INTRODUCTION

Fetal arrhythmias are detected in at least 2% of unselected pregnancies during the routine obstetrical ultrasound. The majority of fetal arrhythmias are benign, but some of them, such as supraventricular or ventricular tachycardia (VT), atrial fibrillation, and atrioventricular (AV) block, may result in low cardiac output, fetal hydrops, and fetal demise. Furthermore, supraventricular tachycardia (SVT) is an important cause of nonimmune hydrops.

Fetal M-mode and Doppler cardiac ultrasound/echocardiography provide the tools to assess fetal cardiac rhythm, enabling diagnosis of the arrhythmia. Despite the development of a magnetically alternative technique (magnetocardiography), ultrasound/echocardiography remains the dominant modality to analyze fetal arrhythmias, which aids assessment of their hemodynamic consequences and

detailed analysis of fetal cardiac anatomy. Detection of fetal heart rate (HR) and identification of arrhythmia are extremely important for appropriate fetal management and treatment, enabling improvements in perinatal outcome.

In this review, the characteristics of irregular heart rhythms, bradycardias, and tachycardias are described, focusing on improved diagnosis by ultrasound. An update on the management and treatment of these arrhythmias is provided through review of many current protocols.

EMBRYOLOGICAL DEVELOPMENT AND PHYSIOPATHOLOGY

During human cardiogenesis, the primitive heart tube produces peristaltic waves of contractions, which

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suggest the presence of a cardiac pacemaker activity. The first morphological signs of sinus node (SN) development are present by 5 weeks of gestation.^[1] The transcription factors *Tbx18* and *Tbx3* are specifically involved in SN development, and *Pitx2* inhibits ectopic SN formation.^[2,3] Indeed, the forced expression pattern of *Tbx3* and deficiency of *Pitx2* are related to the development of ectopic pacemaker tissues and to a dual SN, respectively.^[4,5] The knowledge of these molecular pathways provides us a better understanding of the abnormal development of the cardiac conduction system and aids genetic counseling.

The AV node is morphologically recognizable when the looping heart divides into atrial and ventricular components, yet the AV node conducts electrical signals before this point. The conduction system is functionally developed at 16 weeks of gestation.^[3] The components of the cardiac electrical conduction system are: 1) the SN, 2) the AV node, and 3) the His-Purkinje system. The role of this system is to generate and propagate the electrical impulse through the myocardium to produce each heartbeat. The SN serves as the cardiac pacemaker, which is located in the upper wall of the right atria (RA). The electrical impulse generated by the SN is conducted through the atrial myocardium to the AV node, where this impulse is delayed briefly before being conducted to the ventricles. From the AV node, the electrical impulse is propagated to the ventricles through the bundles of His (bundle of His and its right and the left branches) and the Purkinje fibers [Figure 1].

Automaticity is a characteristic of the cardiac conduction system (SN, AV node, and Purkinje fibers), which means that this system is self-excitable. Automaticity is the result of the inward flow of ions in this group of cells and the biophysical properties of their membranes.^[6] This mechanism is described in Figure 2. The velocity of the depolarization is increased at the SN, and this contributes to its pacemaker characteristic. A better understanding of cardiac electrophysiology is extremely important since arrhythmias result from abnormalities in the generation and/or conduction of electrical impulses. In addition, the types of arrhythmia are classified into irregular rhythms, bradyarrhythmias, and tachyarrhythmias.

THE SONOGRAPHIC PRENATAL DIAGNOSIS OF ARRHYTHMIAS

The postnatal diagnosis of cardiac rhythm is based on the electrocardiogram (ECG). However, determination of the cardiac electrical impulse of the fetus by a conventional ECG has failed. Fetal magnetocardiography (fMCG) is a noninvasive technique for recording the electrical activity of the fetal heart, analogous to the ECG. The fMCG opens a new window into the assessment of

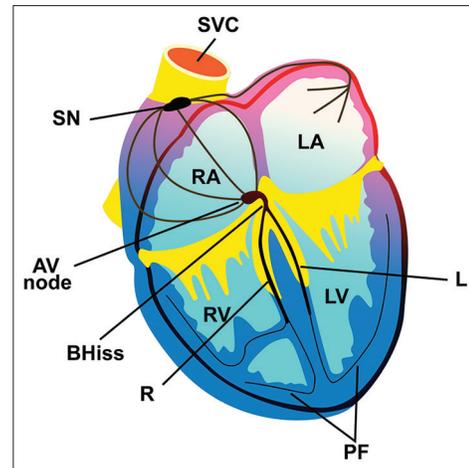


Figure 1: The electrical cardiac conduction system. SN: Sinus node; AV: Atrioventricular node; BHiss: Bundle of His; L, R: Left and right bundle branches; PF: Purkinje fibers

fetal heart electrophysiology by enabling the analysis of T waveforms and measurement of the QT interval. Although this technique is especially important for elucidating the mechanisms of tachyarrhythmias and identifying some high-risk conditions such as long-QT syndrome, it is still a very expensive method.^[7,8] Hence, this technique has limited clinical applicability, and assessment of fetal cardiac rhythm is more frequently performed using cardiac Doppler ultrasound.

The electrical events of the cardiac cycle (atrial and ventricular systole and diastole) can be assessed using ultrasound. During atrial systole, the atria contract and pump blood to the ventricles (active ventricular filling), corresponding to the A wave in the Doppler record of the AV valves, by conventional or tissue Doppler, and in venous Doppler (pulmonary vein, vena cava, and ductus venosus) [Figure 3]. The A wave corresponds to the P wave of the ECG. At the start of the ventricular systole (the isovolumetric contraction phase), the AV and semilunar valves are closed until the fast filling phase, in which the ventricles begin to contract. This corresponds to the isovolumetric contraction time that can be measured using Doppler ultrasound recording [Figure 4]. In sequence, even during the ventricular systole, the ventricle pressures increase adequately to open the aortic and pulmonary valves and eject blood (ejection phase). The aortic or pulmonary flow Doppler ultrasound wave marks the ventricular systole and corresponds to the QRS complex of the ECG. After ejection, the ventricles start to relax (ventricular diastole), which consists of two phases: the isovolumetric relaxation and the ventricular filling. At the start of the ventricular diastole, the valves are closed (isovolumetric relaxation time) until the ventricle pressures drop below atrial pressure. Consequently, the AV valves open and the ventricles fill passively, which corresponds to the E wave in the Doppler record of the AV valve flow [Figure 4].^[9]

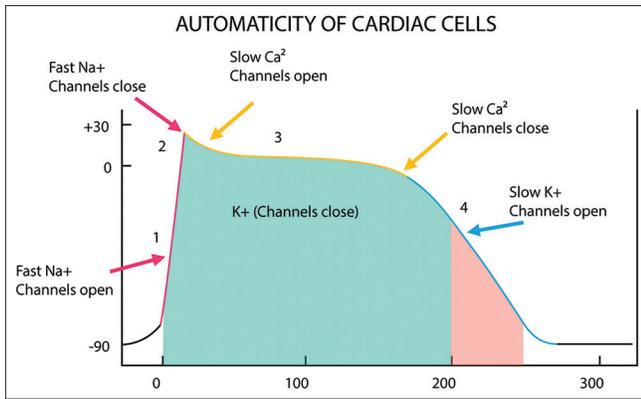


Figure 2: Automaticity of the electrical system cells is related to Na + influx (Na + funny channels) and inactivation of K + channels, which turn the thymidine monophosphate of these cells less negative than the contractile cardiac cell

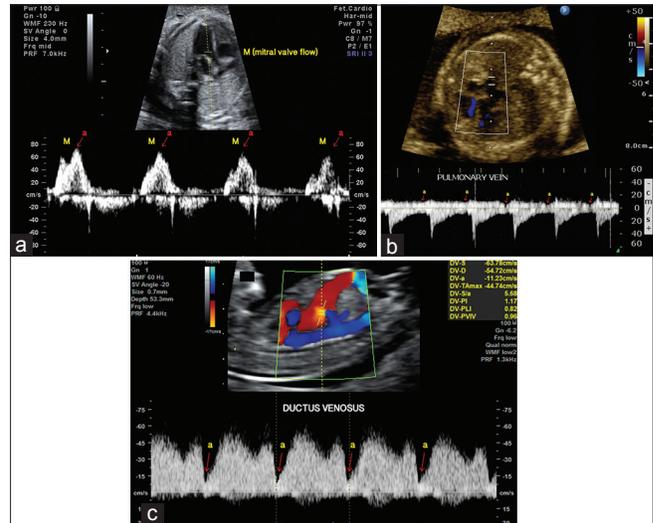


Figure 3: Doppler recording representing atrial (a) contractions. a: input flow A-wave (mitral valve), b: pulmonary vein Doppler A-wave and c: DV Doppler A-wave. (a): atrial contraction

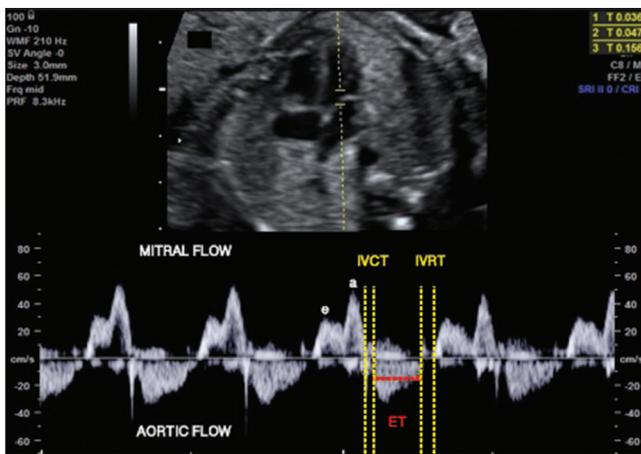


Figure 4: Doppler of input and output ventricular flow with the mechanical phases of the cardiac cycle, which involves systole and diastole. Isovolumetric contraction time, rapid ventricular filling (E wave), slow ventricular filling (A wave); ET: Ejection time; IVRT: Isovolumetric relaxation time

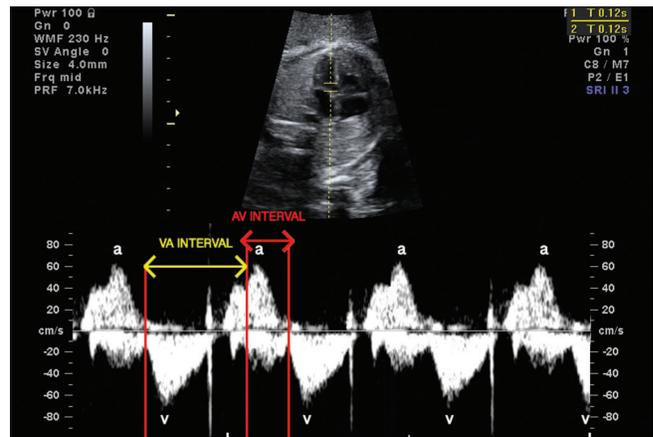
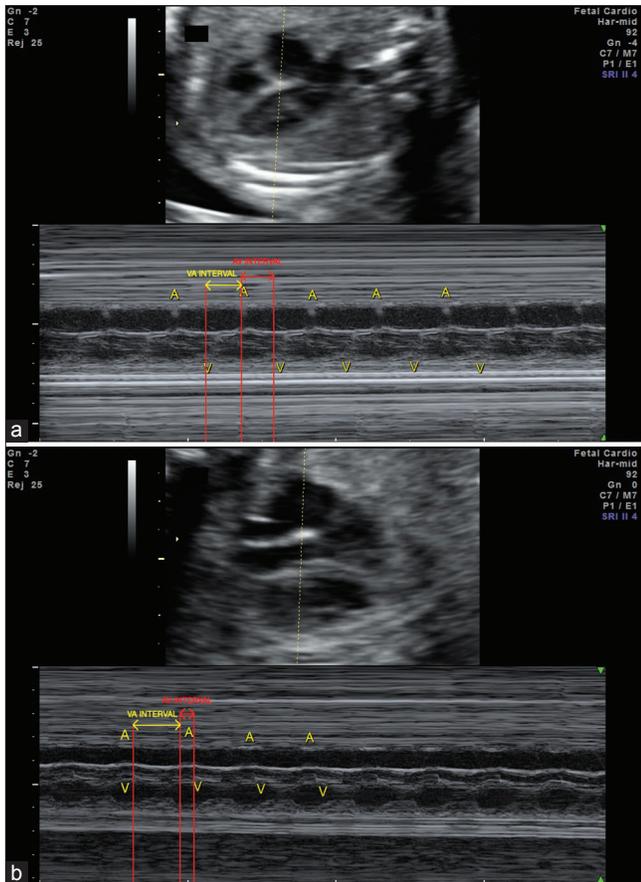


Figure 5: Doppler recording of mitral and aortic flow showing how to measure the AV and VA intervals (analogous to the electrical PR and RP ECG intervals, respectively). A: Atrial contraction; V: Ventricular contraction; AV: Atrioventricular interval time; VA: Ventriculoatrial interval time; HR: Fetal heart rate

Therefore, fetal HR and the relationship with atrial and ventricular cardiac electrical impulses can be assessed by analysis of the Doppler ultrasound record of the AV inflow/outflow waves or by M-mode ultrasound recording of atrial and ventricular wall movements. Measurement of the time interval between atrial and ventricular systole by Doppler permits the indirect assessment of cardiac events. The AV interval, which is the time between atrial and ventricular contraction, can be measured from onset to the A wave onset of the outflow ventricular wave (V wave) Doppler [Figure 5]. The ventriculoatrial interval (VA) is the interval from the V to the A wave. Using M-mode, a similar approach can be performed using atrial wall movements as the A wave and ventricular wall movements as the V wave [Figure 6a]. The AV and VA intervals represent mechanical analogs to the electrical PR and RP intervals of the ECG. These intervals are particularly important for analyzing AV conduction and detailed fetal cardiac rhythm.

HOW TO EVALUATE CARDIAC RHYTHM BY ULTRASOUND/ECHOCARDIOGRAPHY?

By placing the M-mode (motion mode) sampling line across the atrial and ventricular walls, atrial and ventricular contractions (A and V) and their relationship can be assessed [Figure 6a]. Alternatively, the M-mode sample can be displayed between the atrium (RA or LA) and the semilunar valve (pulmonary or aortic valve) [Figure 6b]. Similar to Doppler ultrasound, M-mode enables measurement of the AV and VA intervals, fetal HR, and AV conduction. Although widely used, traditional M-mode assessment becomes impaired during the first trimester and in adverse situations such as unfavorable fetal position, in hydroptic fetuses with cardiac contractile dysfunction,



Figures 6: M-mode ultrasound recording showing how to measure the AV and VA interval times by: (a) Atrial and ventricular wall movements and (b) atrial wall movement and the aortic or pulmonary valve movement (A); atrial wall movement (=atrial contraction); (V) ventricular wall movement or aortic valve movement (=ventricular contraction); Ao: Aortic valve; AV: Atrioventricular interval time; VA: Ventriculoatrial interval time

and in obese pregnant women. However, the dual or anatomic M-mode (AMM) has been used in case of difficult fetal lie where it is often difficult to obtain good quality tracings of atria and ventricles by standard M-mode views. AMM is an imaging tool that enables more accurate placement of the M-mode cursor by providing simultaneous two-dimensional real-time images.

Simultaneous recording of the atrial and ventricular waves can also be obtained using Doppler ultrasound.^[10] Conventionally, the sample volume is placed in the ventricular inflow and outflow tracts (mitral and aortic flows or tricuspid and pulmonary artery flows), which reflects the atrial and ventricular contractions [Figure 7]. Other sampling sites are as follows: (1) The superior vena cava (SVC) and aortic artery flow by rotating 90° from the 4-chamber view [Figure 8a] and (2) the pulmonary venous and pulmonary arterial Doppler on 4-chamber view [Figure 8b]. In both, a wave of the pulmonary vein or SVC corresponds to atrial contraction (A), and the pulmonary artery or aortic flow represents the ventricular contraction (V).

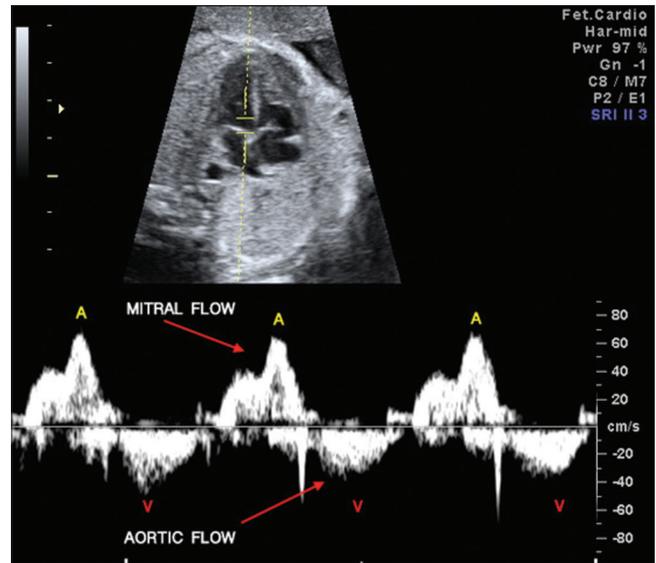


Figure 7: Left outflow tract view showing how to assess the atrioventricular relationship by analysis of the inflow tract and the outflow tract Doppler waves. A: Atrial contraction; V: Ventricular contraction

In the presence of an arrhythmia, some important features should be evaluated: (1) HR, (2) rhythm regularity, (3) AV relationship, and (4) AV and VA intervals. Fetal HR can be calculated by measurement of the interval between atrial or ventricular contractions using the A or V Doppler waves or the atrial or ventricular wall movements (M-mode tracings). Although HR can be manually calculated, in general the ultrasound equipment calculates fetal HR automatically by measuring 1 or 2 cardiac cycles. The normal cardiac rhythm is regular, with similar atrial and ventricular HR (1:1 AV relationship) ranging from 100 to 180 bpm, which may vary depending on the gestational age. Doppler assessment of fetal PR interval can be performed by measurement of the AV interval, with normal reference values ranging from 90 to 150 ms.^[11,12] As a detailed analysis of AV conduction is extremely important to differentiate the types of bradyarrhythmia, AV and VA intervals comparison is also fundamental to diagnosing the type of tachyarrhythmia. Unlike from reentry SVT and VT, in which the VA interval is shorter ($VA < AV$), the VA interval is longer in cases of SVT with an atrial ectopic focus.

In addition, in fetuses with arrhythmia, assessment of cardiac function and detailed anatomical cardiac examination should be performed by echocardiography or cardiac screening ultrasound. Importantly, sustained fetal bradycardia or tachycardia may cause fetal heart failure, nonimmune hydrops, and even death. The cardiovascular profile score has been used as a heart failure score. This score includes some ultrasound markers of cardiac function such as ventricular shortening fraction, valvar regurgitation and ventricular

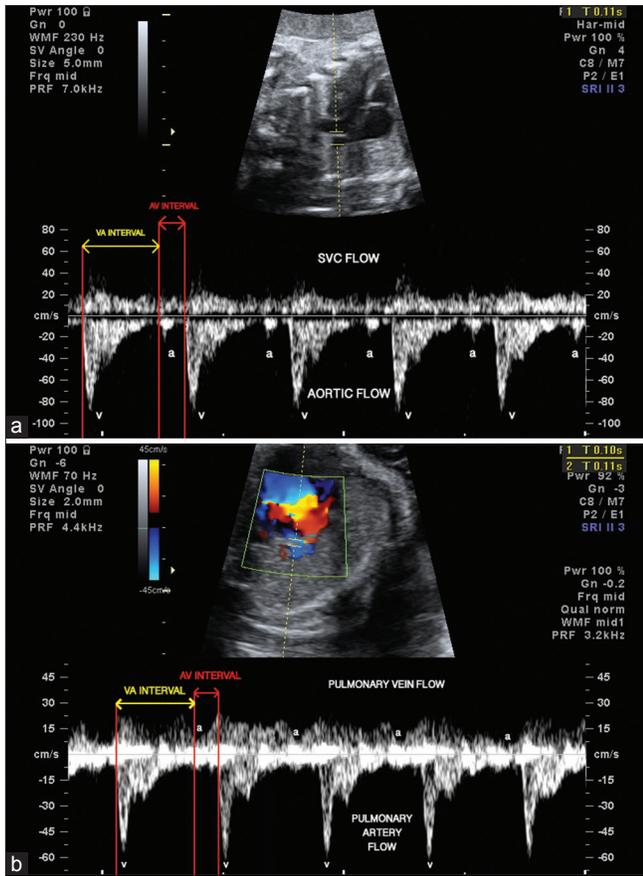


Figure 8: (a) Analysis of AV conduction via analysis of superior vena cava and aortic Doppler waves, (b) Doppler recordings of pulmonary vein and artery showing how to analyze AV conduction and measure the AV interval. A: Atrial contraction; V: Ventricular contraction; AV: Atrioventricular interval; M: Mitral valve flow Doppler wave; Ao: Aortic valve flow Doppler wave; PV: Pulmonary vein flow Doppler wave; PV: Pulmonary artery flow Doppler wave

filling pattern venous (ductus venosus-DV or inferior vena cava-IVC) and umbilical cord Doppler, cardiac biometry (cardiac/thoracic area ratio), and signs of hydrops [Figure 9].^[13] A score of 10 is considered normal and values <7 indicate increased perinatal morbidity and mortality.^[14] The progression of congestive heart failure to the hydropic state is related to an elevation of venous pressure resulting in an increased capillary permeability and edema. The prognosis for a fetus with arrhythmia and hydrops is aggravated, decreasing the therapeutic options.^[15] Although rare in cases of tachyarrhythmia, structural cardiac defects are present in about 50% of fetuses with complete heart block (CHB), and they are another feature of poor prognosis.^[16] Left atrial isomerism, congenitally corrected transposition of great arteries, and AV septal defect are the most common anatomical cardiac malformations associated with CHB.

IRREGULAR RHYTHM

Irregular sinus rhythm at normal HR occurs with atrial or, less frequently, with ventricular premature

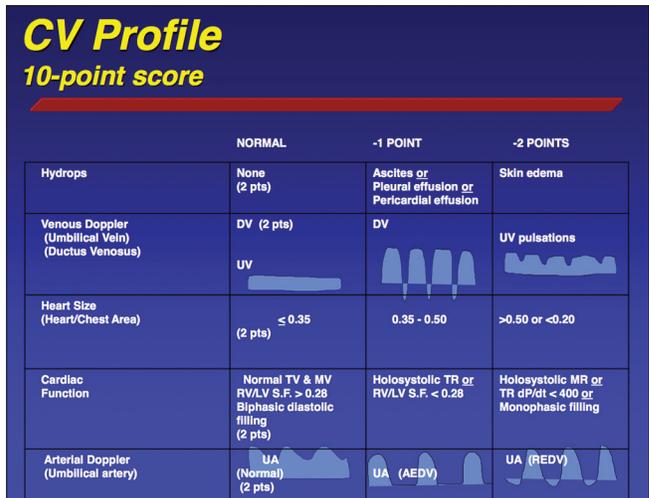


Figure 9: Parameters used in the cardiovascular score for fetal conditions involving risk of heart failure

contractions (PCs), which are clinically benign if brief and isolated and are commonly identified during the third trimester. If an extrasystole follows every sinus beat, it is termed bigeminy, if it follows every third beat, it is termed trigeminy, and if it follows every fourth beat, the rhythm is quadrigeminy.

EXTRASYSTOLES OR PREMATURE CONTRACTIONS

Extrasystoles or PCs are the more common type of fetal arrhythmias and typically occur in the second and third trimesters. Premature atrial contractions (PACs) are extra beats in which the ectopic focus originates in the atria, and premature ventricle contractions (PVCs) are those that originate in the ventricles.

In utero, the prevalence of PAC to PVC is 10:1 and PACs are difficult to distinguish from PVCs. A premature ventricular beat is not preceded by an atrial contraction (no A wave). The PACs may be followed by a ventricular contraction (V wave) when conducted to the ventricles, or not, in cases of blocked PACs [Figures 10a and b]. Indeed, in non conducted PAC there is a longer compensatory pause and this feature would be helpful for differentiating PVCs from PACs.

Fetal ectopy is associated with congenital cardiac defects in approximately 1% of cases, and fetal echocardiogram is recommended. The most common heart defects are cardiac malformations, myocardial diseases, and intracardiac tumors.^[17]

In general, isolated PACs or PVCs do not require antiarrhythmic therapy, and in the majority of cases, these arrhythmias resolve spontaneously before delivery. Despite this, in a small minority of cases, around 2%–3%, the extrasystoles are multiples (couplets), which increase the risk for a sustained SVT in ≈10%.^[18] In these

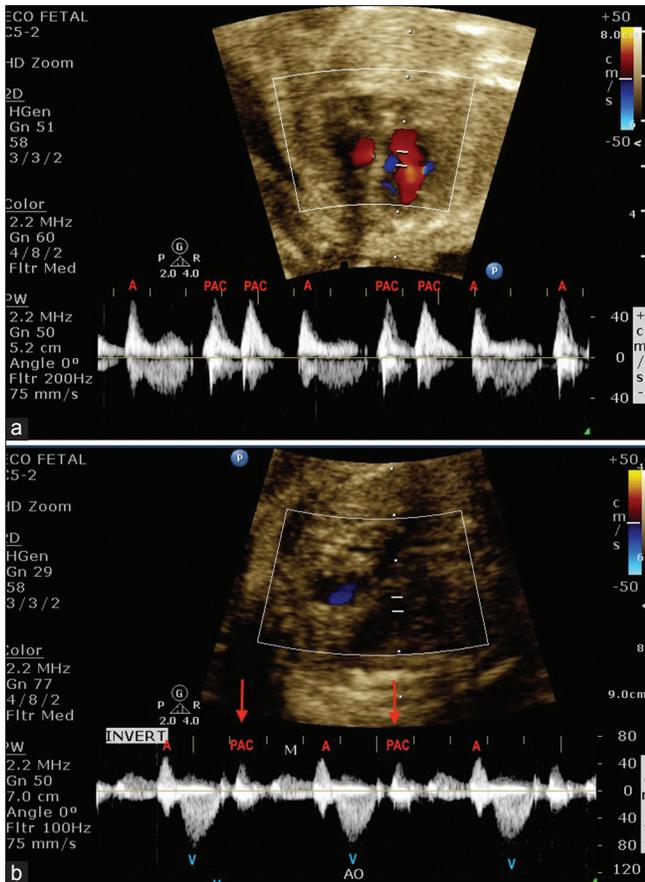


Figure 10: Blocked atrial bigeminy frequently has a variable atrial rhythm, with a shorter AA time interval, between the conducted and following blocked atrial beats (a), alternating with a clearly longer AA time interval between the blocked and following conducted beat (b)

cases, weekly fetal HR auscultation by the obstetrician or maternal-fetal specialist until resolution of the arrhythmia is recommended.^[19] The bigeminal blocked PACs, also known as blocked atrial bigeminy (BAB), often produce a low ventricular fetal HR, ranging from 70 to 90 bpm [Figure 10a and b]. It has not been associated with hydrops, and no treatment is required. BAB is frequently misdiagnosed as second-degree AV block (AVB) and should be correctly identified to avoid management mistakes.

TACHYARRHYTHMIAS

Fetal tachycardia is defined as HR > 180 bpm. Based on its persistence, it can be classified as sustained when the arrhythmia is present for more than 50% of the examination time or intermittent when periods of tachycardia alternate with predominantly normal HR.

According to the electrophysiological levels of the heart, the tachyarrhythmias are subdivided into sinus tachycardia (ST), atrial tachycardia (atrial flutter [AF] and atrial ectopic tachycardia), conduction system tachycardia (AV re-entry tachycardia, junctional

tachycardia, and AV nodal reentry tachycardia), and VT. For clinical practice in general, this classification can be summarized into: 1) ST, 2) SVT, which includes atrial and conduction system types, and 3) VT. SVT is the most common form of fetal tachycardia (70%–75%), whereas VT is the rarest.^[20]

Persistent fast HR may cause fetal heart failure, nonimmune hydrops, and polyhydramnios. Furthermore, maternal complications may occur with sustained fetal tachycardia such as mirror syndrome, which is also known as Ballantyne's syndrome. This is a pregnancy complication that combines fetal hydrops and maternal preeclampsia. Moreover, the diagnosis of tachycardia type should be performed to enable appropriate treatment decisions and minimize complications.

Sinus tachycardia

ST is characterized by fetal HR >180 bpm and more often, <200 bpm with normal AV conduction (1:1). Therefore, ST is characterized by similar atrial and ventricular rates with some variability [Figure 11]. Sustained ST is usually related to fetal distress and pregnancy conditions such as thyrotoxicosis (17% of fetuses in mothers with thyrotoxicosis), anemia, fetal hypoxia, maternal medication (β -agonists), and infections such as chorioamnionitis and cytomegalovirus.^[21] No specific antiarrhythmic therapy is indicated. Indeed, the underlying cause of ST should be identified and treated.

Supraventricular tachycardia

The most common SVT type is related to a fast conducting accessory pathway (re-entrant SVT) and in general, is initiated by an ectopic cardiac beat. In reentrant SVT, the HR usually ranges between 220 and 300 bpm, with a 1:1 AV relationship. The functional-anatomic substrate of the re-entrant SVT consist of presence of an accessory electrical conduction pathway through which the electrical impulse passes from the atrium to the ventricle by the AV node and returns by this route to the atrium in a circular movement (dual pathway). Consequently, conduction of the electrical pulse by the accessory pathway controls the cardiac rhythm with a fast HR. In general, in reentrant SVT, the electrical circuit uses retrograde accessory pathway conduction (ventriculoatrial); conversely, normal electrical conduction uses the antegrade AV node pathway conduction (AV) [Figure 12]. As the retrograde accessory pathway conduction is fast, the atrium is excited shortly after the ventricle, which generates a short VA interval on Doppler or M-mode ultrasound (VA < AV) [Table 1].

Due to the immaturity of the fetal myocardium, accessory pathways occur more frequently *in utero*. Accessory electrical pathways may occur in different locations of the myocardium. Yet another type of SVT is

Table 1: The characteristics of the main types of tachycardia

Tachycardia	Rhythm	AR	AV conduction	VR	AV interval
Re-entrant SVT	Regular	220-300	1:1	220-300	VA < AV VA >70<100 ms VA > AV VA >100 ms
Atrial ectopic tachycardia	Irregular (or chaotic)	>160-250	1:1	Variable	
Atrial flutter	Variable	350-500	2:1, 3:1, 4:1	Variable VR < AR	
JET	Regular	180-240	<1:1 or 1:1	180-240	VA ≥ AV >100 ms VA < AV
VT	Variable	Variable VR > AR	<1:1 or 1:1	180-300	
ST	Regular	180-200	1:1	180-200	AV=VA

SVT: Supraventricular tachycardia, JET: Junctional ectopic tachycardia, VT: Ventricular tachycardia, ST: Sinus tachycardia, AR: Atrial rate, VR: Ventricular rate, AV: Atrioventricular interval time, VA: Ventriculoatrial interval time

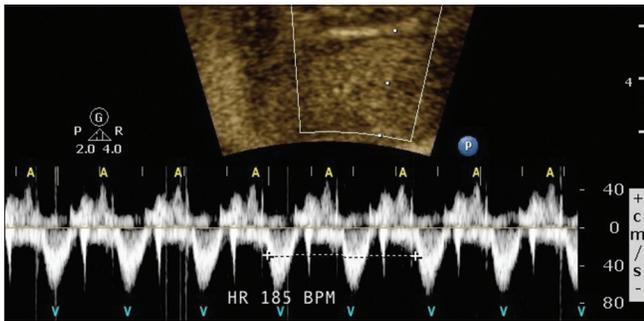


Figure 11: Sinus tachycardia. Simultaneous left ventricular inflow and outflow Doppler wave showing the 1:1 atrioventricular relationship at a rate of 185 bpm

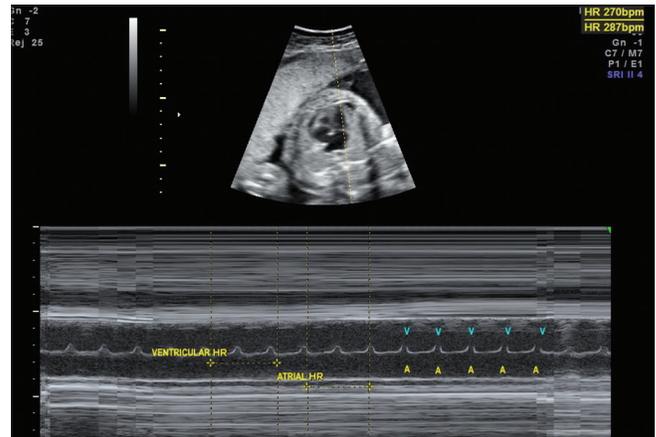


Figure 12: Re-entrant supraventricular tachycardia with HR of 287 bpm M-mode tracing showing the 1:1 atrioventricular conduction. A: Atrium wave; V: Ventricular wave; HR: Heart rate

the AV nodal reentry tachycardia, in which the circuit forms within or immediately adjacent to the AV node. Another mechanism of SVT is an ectopic focus located in the atria. It is a type of SVT known as atrial ectopic tachycardia in which one or more atrial ectopic foci exist with HR ranging from 150 to 250 bpm and a longer VA interval (VA > AV) [Table 1].

In many centers, the first choice to treat fetal SVT is transplacental digoxin, especially in reentry SVT (short VA SVT).^[19] Digoxin is a cardiac glycoside with renal excretion, necessitating dose adjustments in cases of maternal renal failure. The measurement of maternal serum levels of digoxin should be performed at least 6–8 h after the last dose (ideal values: 2–2.5 ng/ml). In other centers, flecainide or sotalol have been used as first-line therapy.^[22,23] Flecainide (class Ic antiarrhythmic agent) blocks the fast sodium channel, which slows the conduction velocity, and sotalol (class III antiarrhythmic agent) blocks β-adrenergic receptors, which prolongs repolarization and the action potential. As with digoxin, the serum levels of flecainide should be monitored (therapeutic levels: 200–1000 ng/ml).^[24]

For second- and third-line therapies, amiodarone has been used alone or in combination with digoxin for refractory tachycardia.^[19,25] As a class III antiarrhythmic agent, amiodarone prolongs repolarization and shows action potential in the hepatic metabolism. However, one

serious effect of its long-term use is fetal and neonatal hypothyroidism, which contraindicates amiodarone use during the first trimester of pregnancy. As digoxin, flecainide, sotalol, and amiodarone are associated with maternal proarrhythmic risk, maternal ECG should be monitored.

Atrial Flutter

AF is caused by an intra-atrial re-entry circuit. AF occurs at a frequency of 25%–30% among all types of tachyarrhythmia.^[20,26] AF is observed only in the third trimester, which is probably related to the large atrial size achieved at 27–30 weeks of gestation, with high vulnerability to atrial extrasystoles.^[20,27] AF can be associated with myocarditis, SSA/SSB isoimmunization, and congenital heart diseases (CHDs).^[28] Ebstein’s anomaly is a type of CHD in which atrial dilatation secondary to tricuspid regurgitation may cause AF. In this type of arrhythmia, the atrial rate ranges from 350 to 500 bpm, with a fixed or varying 2:1, 3:1, or 4:1 AVB, resulting in a slower ventricular rate [Table 1].

In fetuses with AF, sotalol is recommended in cases with hydrops.^[19,26] Digoxin is also recommended, and amiodarone may be considered.^[19,25]

Ventricular tachycardia

VT is extremely rare during fetal life. In general, there is an AV dissociation relationship, with ventricular rates ranging from 180 to 300 bpm in excess of atrial rate. However, in a few cases of VT in which there is a retrograde 1:1 VA conduction, the ventricular and atrial rates are similar (1:1), making it almost impossible to differentiate these types of VT from SVT by fetal cardiac ultrasound. In VT, the Doppler wave velocities of the umbilical cord are low and the VA interval is shorter ($VA < AV$) [Table 1]. The electrophysiological mechanism of this tachycardia is an ectopic ventricular focus due to inflammation (cardiomyopathy) or abnormalities of the myocardial oxygen supply. Myocardial hypoxia in fetuses is related to myocardial hypertrophy secondary to VA valves stenosis or from cardiac tumors such as hamartomas. Furthermore, VT is associated with long-QT syndrome, a genetic ion channel disease. This condition should be strongly suspected when the tachycardia occurs in combination with periods of bradycardia and AV heart block. However, the prenatal measurement of QT interval is only possible by fMCG.

In sustained VT, maternal intravenous magnesium therapy is recommended as first-line treatment at fetal HR >200 bpm. It is advised that intravenous lidocaine, oral propranolol, or oral mexiletine is added to magnesium, as the latter is a short-duration treatment (<48 h). Flecainide, sotalol, and amiodarone should be avoided if long-QT syndrome is suspected.^[22, 29-33] Furthermore, when the VT is related to isoimmunization or myocarditis, dexamethasone, and intravenous infusion of γ -globulin (IVIG) have been used.^[34]

Rare tachycardias

Inappropriate sinus tachycardia

Inappropriate ST (IST) is an exceptional cause of fetal tachyarrhythmia with only a few reports *in utero*. The possible etiologies include a primary abnormality of the SN or an autonomic nervous system disorder.^[31] Similar to ST, in IST the AV conduction rate is 1:1; however, the HR is higher than in ST (>200 bpm). Measurements of AV and VA intervals aid the differential diagnosis of re-entry SVT, while, in the latter, it is possible to identify a short VA interval ($VA < AV$). In IST, an exacerbated increase in HR during fetal movements may suggest the differential diagnosis from ST; however, it remains a challenge in fetuses. Unlike ST, IST is difficult to control and should be treated due to the deleterious effects caused by a sustained, fast fetal HR.^[32] Postnatally, the most used drugs for the treatment of IST are beta-blockers.

Junctional ectopic tachycardia or Coumel tachycardia

Junctional ectopic tachycardia (JET) is a type of SVT occurring due to an AV re-entry via a right posteroseptal

accessory pathway with a 1:1 AV relationship, a HR ranging from 180 to 240 bpm, and a longer VA interval ($VA > AV$), allowing differentiation from other SVT types. In JET, a reentry pathway with slow conduction back to the atrium explains the long VA interval and the incessant behavior. Fetal JET has been associated with SSA isoimmunization, even in the presence of AVB.^[33] The treatment for JET is similar to most of the SVT (sotalol and flecainide), although digoxin is not recommended and amiodarone has been used.

Chaotic or multifocal atrial tachycardia

It is a rare tachycardia that is usually seen late in the second or third trimester of pregnancy and can be associated with Costello syndrome. Increased nuchal thickness, polyhydramnios, short femurs and humeri, and myocardial hypertrophy associated with atrial tachycardia should create suspicion of Costello syndrome.^[34] Atrial ectopic tachycardia causes persistent variable atrial rates of 180–220 bpm with a 1:1 conduction pattern and an average HR of 160–200 bpm if associated with heart dysfunction. This type of atrial tachycardia is difficult to treat, and the treatment goal is to control HR. Digoxin is the first-line therapy in fetuses without hydrops or ventricular dysfunction. Sotalol and flecainide may be considered.

In utero management and therapeutic protocols for fetal tachycardia

Fetal tachycardia is an important cause of fetal nonimmune hydrops, premature delivery, and perinatal morbidity and mortality. Therefore, sustained fetal tachycardia should be considered an emergency in fetal cardiology and treatment should be promptly instituted.

Pharmacological treatment is recommended for all sustained tachycardia, except for a near-term fetus and for ST. In general, delivery is recommended for near-term fetuses. Antiarrhythmic medications are used in transplacental (given orally or intravenously to the mother) or fetal therapies (umbilical cord). The latter can be considered only in hydropic fetuses, especially if the biophysical profile score (BPS) is altered.

During antiarrhythmic therapy, the fetus should be closely monitored by BPS and fetal echocardiography. Doppler velocimetry in umbilical and middle cerebral arteries are not useful for fetal surveillance during tachycardia. However, in cases of ST, the Doppler of uterine arteries may reflect fetal distress due to placental dysfunction. Furthermore, close monitoring of the mother for antiarrhythmic medication side effects should be performed using maternal ECG, maternal vital signs, and serum levels of the antiarrhythmic medications, electrolytes, and vitamin D.^[19, 26]

The precise treatment and management of fetal tachyarrhythmias may vary from center to center. The

algorithm in Figure 13 describes the reasonable drugs used for *in utero* therapy of tachycardias based on review studies.^[19,20,23]

BRADYARRHYTHMIAS

According to the American College of Obstetrics and Gynecology, fetal sinus bradycardia is defined as a sustained fetal HR lower than 110 bpm over at least a 10 min period.^[35] Unfortunately, in many prenatal evaluations for low-risk fetuses of any gestational age, the heartbeat is merely checked as being present without documentation of its rate, which is a primary mistake. Importantly, fetal HR is gestational age-dependent, and bradycardia duration should be considered.^[26] Examining electronic cardiocotographic records from 4412 healthy singleton fetuses, Serra *et al.* derived percentiles for fetal HR from 25 weeks' gestation onward.^[36] On average, ventricular rates were below the fifth percentile if they were <130 bpm at 25 weeks of gestation, <120 bpm at 30 weeks gestation, or <110 bpm at term.^[36]

Clinically insignificant episodes of fetal bradycardia are frequent; these are transient fetal decelerations that resolve within minutes, are often noted in the second trimester, and are thought to be benign.^[26] Less common, but more concerning for both the parents and the physician, is the new detection of an abnormally slow fetal HR that does not resolve during the pregnancy clinical examination.^[37] These episodes of persistent fetal bradycardia may be due to sinus, low-atrial, or junctional bradycardia, long-QT syndrome and other ion channelopathies, BAB, or AVB.^[26]

Fetal sinus and low-atrial bradycardias

Persistent fetal bradycardia is relatively rare. The basic mechanisms include congenital displaced atrial activation, acquired damage of the SA node, ion channel dysfunction, and secondary suppression of the SN rate.^[19] SN rates can be suppressed due to, for example atrial isomerism, inflammation and fibrosis in a normal SN, viral myocarditis or collagen vascular disorders (SSA/Ro and/or SSB/La antibodies), maternal treatment with beta-blockers, sedatives, or other medications,^[38] rare metabolic disorders (e.g. Pompe's disease), or sinus bradycardia due to idiopathic origin, neck stretch, or other autonomic causes.

In fetal sinus bradycardia, the atrial and ventricular mechanical events are equally slow and occur with a normal 1:1 AV relationship.^[39] In low-atrial bradycardia, short PR interval is present in the ECG. Low-atrial mechanisms are seen in left atrial isomerism due to the absence of the SN.^[40]

Fetal sinus and low-atrial bradycardias usually demonstrate HR reactivity even in the presence of serious underlying conditions; however, this reactivity may be blunted due to a reduction in the autonomic influences.^[40] Neither sinus nor low-atrial bradycardia require specific treatment and are not generally associated with hemodynamic compromise at the time of birth. However, since 40% of fetuses with sinus bradycardia have associated long-QT syndrome, neonatal ECG screening is recommended considering this condition's inherent autosomal-dominant transmission.^[41-43]

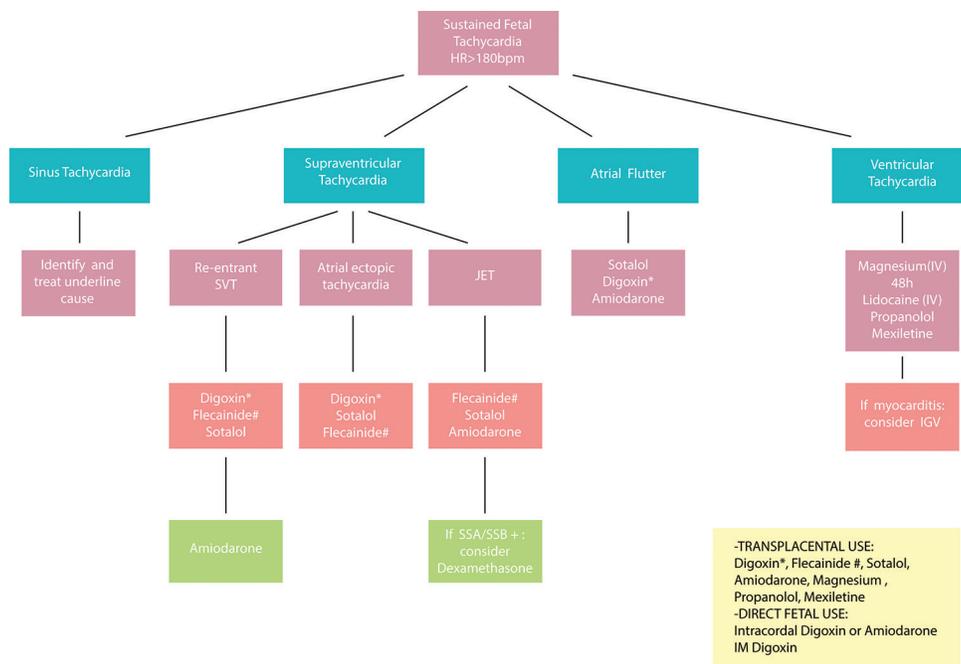


Figure 13: In utero tachycardia treatment algorithm

Long-QT syndrome and other ion channelopathies

Persistent fetal bradycardia resulting from long-QT syndrome may present as isolated mild sinus bradycardia, 2:1 AVB,^[44-55] torsades de pointes, or VT.^[29,41]

Management of a fetus with suspected long-QT syndrome includes close observation, postnatal evaluation, and measurement of QTc by fMCG or fetal ECG, if available.^[56] Fetal treatment is not recommended for bradycardia; however, torsades de pointes and VT require treatment.^[41] Maternal electrolyte abnormalities, especially hypomagnesemia and hypocalcemia, as well as drugs and anesthetic agents that lengthen the QT interval, should be avoided. An updated list of these drugs can be found on several websites, most notably www.torsades.org.^[19]

Atrial bigeminy with blocked premature beats

In approximately 30% of cases of sustained fetal bradycardia, the mechanism is BAB, resulting in a well-tolerated reduction in the ventricular rate, which usually converts spontaneously to normal sinus rhythm before delivery.^[45,48,49] No treatment is required, although SVT has been documented in $\approx 10\%$ of these cases.^[19]

BAB frequently has a typical atrial rhythm with an alternating, shorter-longer AA time interval.^[48-50] Furthermore, the isovolumetric contraction time is shorter, which can improve the differential diagnosis with 2:1 AVB.^[51]

In a structurally normal heart, a fetus with nonconducted atrial bigeminy can compensate for a decreased ventricular rate by increasing the ventricular stroke volume, leading to spontaneous resolution without treatment.^[37,52]

Fetal atrioventricular block

The incidence of congenital AVB is between 1 in 15,000 and 1 in 20,000 births.^[40] Approximately half of all AVB cases are caused by associated CHD, and the remaining cases that have normal cardiac structure are often caused by maternal SSA antibody.^[16,53,54]

Reference values have been defined, and surveillance protocols have been designed for implementation between 16 and 24 weeks of gestation, the period during which the fetus is at the highest risk of developing complete AVB (CAVB).^[37,55]

In clinical practice, there are three grades of heart block: First, second (incomplete), and third (complete block) degrees.^[27]

Diagnosing first-degree atrioventricular block

In first-degree AVB, all impulses are conducted from the atria to the ventricles, but AV conduction time is prolonged beyond the upper limit of normal. Doppler flow velocimetry from the mitral valve aortic outflow (MV-Ao)

or SVC-Ao are the most widely used modalities for detecting prolonged AV conduction [Figure 14]. The methods have been validated^[11,55-58] and reference values have been established.^[55,56,59-61]

AV intervals increase with gestation and decrease with increased HR.^[55,59-61] Increased HR and prolongation of the AV interval also lead to difficulties in correctly identifying the starting point of the MV-Ao measurement, making the SVC-Ao a superior method in these fetuses.^[62]

Diagnosing second-degree atrioventricular block

Second-degree AVB is extremely rare. It is a failure to conduct some atrial impulses to the ventricles. In Mobitz Type I (Wenckebach) second-degree AVB, there is a progressive lengthening of AV conduction until an isolated impulse is blocked. Mobitz Type II second-degree AVB is characterized by a sudden block of an isolated impulse without prior lengthening of the AV conduction time.

The HR in second-degree AVB can be regular if ventricular beats are “dropped” in a regular 2:1 or higher AV ratio.^[37] Blocked premature beats and AVB are characterized by an atrial rate that is faster than the ventricular rate.^[37] However, BAB typically resolves spontaneously, unlike AVB, which is typically associated with structural heart disease or maternal anti-Ro/SSA and anti-La/SSB autoantibodies.^[37]

M-mode recordings are frequently unsuitable for diagnosing cases of 2:1 AVB.^[53] Techniques that simultaneously record arterial and venous flow are needed to differentiate 2:1 AVB from BAB and CAVB.^[49,50] With pulsed-wave Doppler, signals can be recorded simultaneously from the left ventricular MV-Ao,^[63] SVC/ascending aorta (SVC-Ao),^[62-64] as well as a pulmonary vein and peripheral pulmonary artery.^[65] A simultaneous recording of arterial and venous flow is optimal but not always suitable to obtain since high-quality images are necessary to differentiate the regularity of atrial rhythm in cases with a 2:1 AVB. To overcome this issue, Sonesson *et al.* found that recordings from the ductus venosus may be useful for distinguishing between 2:1 AVB and BAB.^[50]

Diagnosing third-degree atrioventricular block

Third-degree AVB or CAVB is a condition where there is no AV conduction, and the atria and ventricles beat independently. A slow ventricular rhythm with AV dissociation is only seen in CAVB [Figure 15].

In CAVB and 2:1 AVB, there is a regular atrial rhythm, and a repeated recording will usually reveal whether the AV time interval remains the same, suggesting 2:1 AVB, or has changed, indicating CAVB.^[52] A HR <60 bpm is strongly indicative of CAVB;^[50] patients with BAB have a HR of 65–90 bpm which is frequently intermittent, and 2:1 AVB results in a HR of 60–75 bpm.^[52]

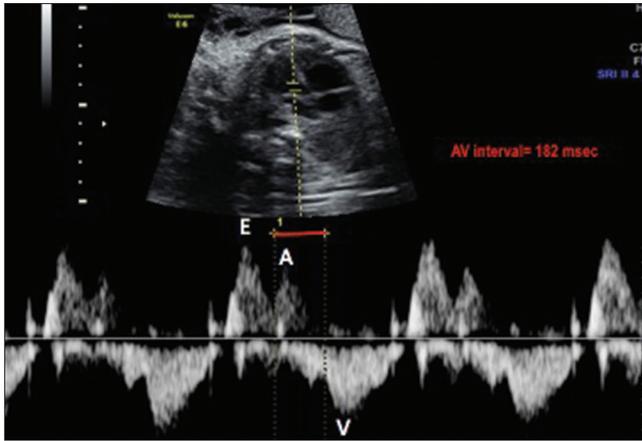


Figure 14: Doppler flow velocity recordings from a fetus with indirect signs of first-degree atrioventricular block at 32 weeks gestation. A recording from the mitral valve (upward) and left ventricular outflow to the aorta (downward). The first vertical line denotes the intersection of the mitral early filling wave (E) and the subsequent wave attributed to atrial contraction (A). The second line denotes the onset of ventricular ejection (V), between which the atrioventricular time interval is measured

In fetuses with CAVB and hydrops or endocardial fibroelastosis, high rates of mortality (6%–20% or more), and morbidity have been described. In addition, life-threatening late-onset cardiomyopathies have also been found.^[66,67]

Congenital AVB can be classified according to etiology of the block as it relates to structural defects, the presence of maternal SSA/Ro or SSB/La antibodies, and block of unclear etiology.

Atrioventricular block and congenital cardiac defects

Congenital cardiac defects associated with AVB include mainly heterotaxy syndromes (left atrial isomerism) and discordant AV connection. These cardiac defects are very complex. In left atrial isomerism, the absence of an SN can lead to low-atrial bradycardia in these fetuses. The right and left chambers are malaligned with the inflow and outflow portions of the heart, resulting in a discontinuity between the AV node and the conduction system.

The prognosis for fetal AVB associated with congenital heart defects remains extremely poor, with a combined fetal and neonatal mortality >80%.^[68] The reason for this poor prognosis is not completely understood. In fetuses with AVB and congenital heart defects who survive into the neonatal period, the hemodynamic response to stress, as in a surgical procedure, is abnormal and often leads to abrupt, profound, and ultimately lethal changes in clinical status.^[27]

Isoimmune atrioventricular block

In the absence of structural heart disease, AVB is mainly secondary to immune-mediated inflammation and fibrosis of the fetal conduction system from maternal SSA/Ro and/or SSB/La antibodies that can cross the

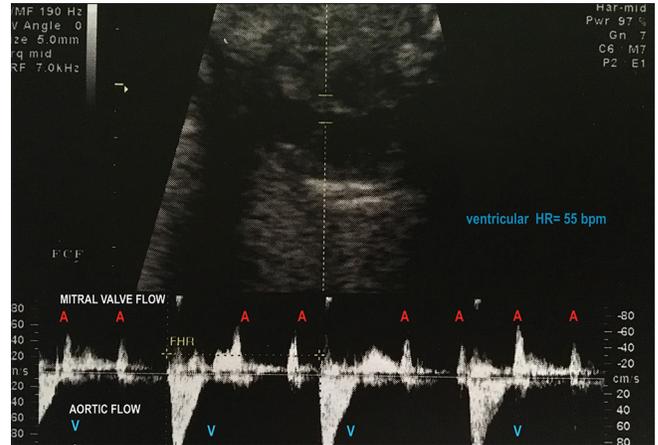


Figure 15: Complete atrioventricular block in a hydropic fetus from a woman with high anti-SSA and anti-SSB antibody titers. Doppler of mitral and aortic flow recordings at 26 weeks of gestation showing the CAVB with 55 ventricular heart rate and 121 atrial heart rate. CAVB: Complete Atrioventricular block, A: Atrial contraction, V: Ventricular contraction; HR: Heart rate

placenta.^[26,37] The incidence of CAVB in patients with SSA/Ro and SSB/La antibodies is approximately 2%–3%. Half of these women are asymptomatic concerning their rheumatologic disorder and are unaware that they carry the antibodies. The risk of recurrence for AVB when a prior fetus has been affected is 19%.^[69] Therefore, in this population, close observation with serial echocardiography is warranted.^[27]

Isoimmune AVB results from placental transfer of autoantibodies produced by the mother that target ribonucleoproteins of unknown function. Autoantibodies that target SSA/Ro and SSB/La are termed “antinuclear antibodies,” but approximately 70% of these ribonucleoproteins are actually situated in the cytoplasmic compartment. The antibodies that produce the most damage to the conduction system are the 48 kDa SSB/La peptide and the two 52 kDa and 60 kDa SSA/Ro peptides.^[70] Initially, an alteration in L-type calcium channels may be reversible but is generally followed by apoptosis and cell death.^[71] This damage targets, but is not confined, to the conduction system.^[26,27,37]

These antibodies enter the fetal circulation in mid-gestation and may elicit progressive destruction of the fetal AV node, myocardial inflammation, and endocardial fibroelastosis in the susceptible fetus.^[37] Other manifestations of SSA/Ro-mediated or SSB/La-mediated cardiac disease include SN dysfunction, bundle branch block, and late-onset rupture of the AV valve chordae.^[47] The evidence is emerging that, in addition to conduction disease, 10%–15% of the affected offspring will have a life-threatening cardiomyopathy. This more extensive injury can occur in utero or postnatally, even as late as 9 years of age.^[69]

AVB is generally not seen before 18 weeks gestation, and the onset is rare after 28 weeks gestation.^[26] Detecting

the onset of fetal AVB in SSA/Ro-positive mothers is a tremendous challenge. Initially, weekly echocardiograms were thought to be adequate to detect a gradual PR prolongation and eventual block; however, some fetuses with normal PR intervals can develop CAVB within days with no preceding first-degree AVB.^[69] By contrast, when first-degree AVB is seen, it rarely progresses to CAVB.^[33,69,72,73] According to Friedman *et al.*, prolongation of the mechanical Doppler PR interval did not precede more advanced congenital AVB and cannot be considered a predictor of early signs of heart block in SSA- or SSB-positive pregnancies. Nonetheless, atrial echodensity and moderate-to-severe tricuspid regurgitation were signs of injury leading to advanced AVB.^[69] Thus, these findings demonstrate the need to have advanced and integrated imaging modalities for fetuses at risk of developing congenital AVB.

Isolated atrioventricular block

Isolated AVB without positive SSA/Ro or SSB/La antibodies is rare, and the etiology of this type of block is not clear.^[27] Isolated AVB appears to have the best long-term prognosis.^[16,26,27] Lopes *et al.* reported that spontaneous regression of AVB in utero is possible in fetuses whose mothers remained seronegative for antinuclear antibodies throughout pregnancy.^[16] Baruteau *et al.* reported interim analysis from the French Multicenter Study that showed a distinct survival benefit for this subgroup.^[42] In this study, 37% of these seronegative AVB fetuses progressed to third-degree AVB during childhood.^[42]

IN UTERO MANAGEMENT AND THERAPEUTIC OPTIONS FOR THE FETAL ATRIOVENTRICULAR BLOCK

Efficacy of prenatal treatment for fetal AVB is limited compared to treatment for fetal tachycardia.^[74] The treatment of fetal bradycardia involves close observation for signs of fetal compromise or distress. Decisions on early delivery and the complications of prematurity should be based on a risk-benefit analysis for both mother and fetus. In general, delivery is recommended for near-term fetuses. AVB treatment depends on the origin, ventricular rate, and presence and degree of heart failure. Beta-adrenergic drugs, steroids, and immunoglobulin are reported to be effective transplacental treatments for fetal AVB (given orally or intravenously to the mother) or fetal therapies (umbilical cord).^[74] Antibody-exposed fetuses should undergo weekly echocardiograms between 16 and 24 weeks of gestation to assess AV chronology.

Beta-adrenergic drugs

The use of β -sympathomimetics (terbutaline, salbutamol, and isoprenaline) to augment fetal ventricular rates (when <55 bpm) and myocardial contractility has been reported, regardless of the immune-mediated or

structural CHB origin.^[75,76] They effectively increase the fetal ventricular rate by approximately 10%–20% and reverse hydrops in some fetuses with AVB.^[74]

Orally administered salbutamol (10 mg t. i. d.) typically increases fetal HR by 5–10 bpm. *In utero*, terbutaline is normally well tolerated, but maternal resting HR around 100–120 bpm and benign maternal ectopy beats have been commonly found.^[76] Other side effects are palpitations and tremor. Unfortunately, although terbutaline may increase fetal rates and prolong pregnancy, no studies have shown a survival benefit. Moreover, fetal pacing has not been shown to be successful in improving survival or prolonging gestation; therefore, at present, this treatment is experimental and not recommended as part of standard care.^[77]

Steroids

The rationale for using steroids is to decrease inflammation,^[74] revert or stabilize incomplete block, and ameliorate hydrops, endocardial fibroelastosis, and myocardial dysfunction.^[27,75,78–82] Isoimmune AVB may benefit from *in utero* treatment with fluorinated steroids, IVIG, or both.^[80–83]

Fluorinated steroids (dexamethasone and betamethasone) are minimally metabolized by the placenta and are useful when direct anti-inflammatory fetal treatment is desired. Although no consensus exists, many clinicians are using dexamethasone 4–8 mg/d. Important complications of dexamethasone that have been reported include growth restriction, oligohydramnios, ductal constriction (also attributed to the collagen vascular disease itself), maternal diabetes mellitus, and central nervous system side effects.^[81–83] In cases of steroid-induced oligohydramnios, the amniotic fluid volume should be carefully monitored throughout gestation and dexamethasone reduced to 2 mg/d at approximately 30 weeks gestation. The long-term effects of steroids, fetal bradycardia, and maternal autoantibodies on the developing human fetus are still largely unknown.^[84]

Despite these potential complications, a trial of dexamethasone for second-degree AVB, or first-degree AVB if there are additional cardiac findings of inflammation (echogenicity, valve regurgitation, cardiac dysfunction, effusion, etc.), may be considered to prevent progression to CAVB; however, its usefulness is not well established^[69] given that studies to date have been retrospective, nonrandomized, and had incomplete follow-up.^[16,82]

An important step before the initiation of dexamethasone is the provision of adequate maternal counseling given the risks and limited data on benefit. The drug should be discontinued if significant maternal or fetal side effects develop. Prospective, randomized trials or a

registry are necessary to establish definitive treatment recommendations for fetal AVB.^[19,37,74]

IVIG, usually administered with dexamethasone, may be considered given that it improved survival when endocardial fibroelastosis or systolic dysfunction was present in one retrospective multicenter study.^[79] The most optimal administration timing and the intervals for repeat dosing remain unknown. IVIG prophylaxis in early pregnancy is not recommended.^[70] Risks of IVIG treatment are mainly exposure to blood products and allergic reactions.

CONCLUSION

Management of fetal arrhythmia is crucial to improving outcomes. Accurate prenatal diagnosis is important for selecting the appropriate prenatal and postnatal treatments. However, there are still many issues regarding the management of both fetal tachycardia and bradycardia, and more useful strategies should be investigated. Therefore, it is fundamental to develop multicenter prospective clinical studies that will direct future treatment for such uncommon conditions.

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Conflicts of interest

There are no conflicts of interest.

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